Attorney Docket No.: 22841-011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#8

In the Reexamination of:	)	
Nicolson et al.	)	
	)	
U.S. Patent No.: 5,760,100	)	**Examiner: V. Jagannathan**
Filed: December 8, 1995	)	
Issued: June 2, 1998	)	**Art Unit: 1714**
	)	
For: Extended Wear Ophthalmic Lens	)	
	)	
Reexamination Proceeding	)	
Control No.: 90/005,283	)	
Filing Date: March 5, 1999	)	

DECLARATION OF LYNN C. WINTERTON
UNDER 37 C.F.R. § 1.132

1. I, Lynn C. Winterton, willfully make the following Declaration regarding the Extended Wear Ophthalmic Lenses as disclosed and claimed in U.S. Patent 5,760,100. I declare and say as follows:

2. I am a Distinguished Research Fellow and presently serve as an R&D Group Leader within the Surfaces Organization of CIBA Vision, a Novartis Company, 11460 Johns Creek Parkway, Duluth, Georgia 30097-1556, and I am a co-inventor of US 5,760,100.

3. I received the degree of Bachelor of Science in Materials Science and Engineering in 1980 from the University of Utah, located in Salt Lake City, Utah and I received the degree of Ph.D. in Materials Science and Engineering in 1984 from the University of Utah, located in Salt Lake City, Utah.

4. I have read and am familiar with the disclosure and presently pending claims of the above-captioned Patent as well as issues raised in the Office Actions issued by the U.S. Patent & Trademark Office dated November 10, 1999 and April 18, 2000.

5. In the Office Action of April 18, 2000, pending claims 1-48, 52, 53 59 and 60 were rejected under 35 U.S.C. § 102 as anticipated by or in the alternative as obvious over US 5,034,461 to I ai et al. (hereinafter Lai '461) pursuant to 35 U.S.C. § 103. Pending claims 49, 51, 54-58 and 61-64 were under rejected 35 U.S.C. § 103 as being unpatentable over Lai '461 in view of either the English language translation of Japanese Patent No JP 6-122779 (hereinafter JP) alone or JP and Hawley's Condensed Chemical Dictionary, Twelfth ed., page 28 (hereinafter Hawley). Pending claims 50 and 61-63 were rejected 35 U.S.C. § 103 as being unpatentable over Lai '461 in view of either US 3,894,129 to Hoffman or US 5,804,107 to Martin.

6. To demonstrate the patentability of the present inventive lenses as taught in US 5,760,100 over the art cited in the reexamination, the following comparative experiments were conducted in accordance with the following procedure.

Contact Lens Preparation and Wettability Results

7. As submitted by Declaration on March 2, 2000, Jacalyn M. Schremmer attempted to reproduce the method disclosed in Example 11 of Lai '461 for the purpose of preparing an IDS3H prepolymer and a copolymer formulated with the IDS3H prepolymer together with dimethylacrylamide (DMA) and tris(trimethylsiloxy)silylpropyl methacrylate (TRIS), in a weight ratio equivalent to 40:30:30, respectively. Contact lenses were then prepared by cast molding this formulation in accordance with the Declaration of Ms. Schremmer.

8. Six of the Lai '461 40:30:30 lenses prepared by Ms. Schremmer, as described above, were stored in a solution of 80%water/20% isopropyl alcohol (IPA) (vol./vol.) to prevent bacterial and fungal contamination and were forwarded to me at CIBA Vision via Gail Kelch.

9. Our work has shown that this water/IPA formulation to be very useful for silicone hydrogels, as well as other lens materials, for this very purpose. The lenses were then exchanged into buffered saline (SoftWear™ Saline)[1] so that sessile contact angles of these lenses could be measured.

10. This is done by using a standard operating procedure within my group. The lens is placed into at least 10 ml purified water for at least 30 minutes. This water is then completely replaced with other purified water in the same volume for the same minimum time. The lens is then placed into SoftWear™ Saline for a minimum of 30 minutes in a minimum of 10ml volume. This solution is also replaced by other SoftWear™ Saline in similar volume. The lens is now considered properly conditioned so that the contact angle can be measured.

11. During the contact angle measurement procedure, the lens is only handled using polyvinyl chloride (PVC) tipped forceps. The PVC has previously been conditioned by boiling it in purified water for a minimum of one hour. The lens is then blotted with a clean-room wiper (no lint) and immediately measured on an automated VCA 2500[2] contact angle instrument using water as the probe solvent.

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[1] SoftWear™ Saline is an isotonic borate buffered saline solution commercially available through CIBA Vision.

[2] VCA 2500 is a contact angle instrument available from Advanced Surface Technologies, Boston, MA.

12. The following data was recorded:

Schremmer Lens Number:	Contact Angle First Measurement	Contact Angle Second Measurement
1	106	106
2	99	95
3	96	96
4	98	96
5	89	93
6	93	94
Average	97	97
Std. Deviation	6	5

13. Contact angle measurements are generally considered by the surface analysis community reproducible within about five degrees of the actual value. This data set is exemplary of this accuracy.

14. It should be noted that the above characteristic non-wetting behavior of both sets of materials was similarly observed by Drs. Hung and Wang, as provided in their Declaration, submitted March 2, 2000. This non-wetting certainly is a surface-material characteristic of the Lai '461 material.

15. In contrast to the Lai '461 lenses, the inventive lenses made in accordance with the embodiments of Examples B-5 and E-12 of US 5,760,100, for example, have a manufacturing specification for contact angle of 65 ± 10 degrees measured at ambient temperature. The inventive lenses are wettable. These results are statistically relevant and are unexpected and superior over Lai '461.

16. From the above contact angle measurements, it would be apparent to one of skill in the art that lenses made according to the materials of Example 11 of Lai '461 are <u>not</u> ophthalmically compatible and thus not suited for use in an ocular environment.

17. It should be noted that the Declaration submitted by David J. Heiler, Ph.D. on March 5, 1999 (hereinafter Heiler Declaration) does not offer any data as to the ocular wettability of lenses made according to the materials of Lai '461.

18. It should be further noted that in Lai's own testimony he indicated that a contact angle above seventy on a material would make it non-wetting; and thus non-utilitarian as a contact lens material.[3]

Wettability as a Criterion for Ophthalmic Compatibility

19. In the ophthalmic arts it is appreciated that the wetting behavior of a given material's surface is an important factor for ophthalmically compatible lenses. Surface wetting is the material's ability to accommodate an aqueous environment by minimizing excess surface energy. Surface wetting, however, is not indicative of lipid adsorption, protein adsorption, lens movement, water or ion permeability of the material, or oxygen transmission of the contact lens candidate.

20. Although surface wetting is necessary for an ophthalmic lens, the reliance on wetting behavior as a criterion for ophthalmic compatibility is utterly insufficient. Ophthalmic compatibility is a state of being, while residing in a biological environment. To be ophthalmically compatible, a contact lens must reside on the eye without significantly interfering or interrupting the existing natural biological ocular environment.

21. Thus, even though one of ordinary skill in the ophthalmic arts would recognize that the material made from Example 11 of Lai '461 in to a contact lens is <u>not</u> suited for intimate contact with ocular tissue or ocular fluid, because of the material's lack of wettability, the following experiments and associated procedures further demonstrate the ophthalmic deficiencies of the Lai '461 materials as contact lenses.

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[3] See pages 166 through 169 of Lai's deposition testimony.

Contact Lens Preparation and Ophthalmic Compatibility Results

22. As submitted by Declaration on March 2, 2000, William Hung, Ph.D. and Guigui Wang, Ph.D. prepared hard-soft-hard urethane prepolymer as set forth in Example 11 of Lai '461 to recreate IDS3H:DMA:Tris, with recited formulation having components in the ratio of 40:30:30 as reported in Table 10 of Lai '461 and prepared lenses of the above copolymer.

23. The Lai '461 40:30:30 lenses prepared by Drs. Hung and Wang were stored in 80:20 (vol./vol.) Water/Isopropyl alcohol prior to testing and were forwarded to me at CIBA Vision via Roslyn Dandridge. This storage method is required in order to prevent microbial contamination of the material as well as prevent the lenses from sticking to the glass storage vials.

24. The lenses were removed from the storage vial and soaked in water for a minimum of 30 minutes and then in SoftWear™ Saline for a minimum of 30 minutes. Clean disposable cups were used for the soaking procedures. The Hung & Wang lenses were then conditioned for In-Vivo and subsequent In-Vitro experiments. For the following In-Vivo experiments, the exemplary Lai '461 lenses were autoclaved in accordance with typical CIBA Vision procedures.[4]

25. To demonstrate the deficiencies of the lenses made according to materials of Lai '461, one of the Hung & Wang lenses, conditioned and autoclaved according to the above procedure, was placed on the surface of a hydroxyethyl methylacrylate (HEMA) lens which had already been placed on one of the eye balls of Dr. Norman Becker[5] in a piggyback arrangement.

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[4] The lenses were autoclaved at 121 °C for 30 minutes.

[5] Dr. Norman Becker is employed by CIBA Vision as a research optometrist.

26. The Lai '461 lens could not be directly placed on the ocular tissue of Dr. Becker, or any other human, because the material and lenses fabricated therefrom were tacky and presented a significant risk of damage to the ocular environment if applied directly to the corneal tissue. Thus, for the safety of the wearer, the Lai '461 lens was placed in a piggyback arrangement in the eye.

27. Ophthalmically compatible lenses manufactured and marketed by CIBA Vision Corporation as Focus™ Night & Day® lenses (made in accordance with the present invention as taught, for example, in the embodiments of Examples B-5 and E-12 of the US 5,760,100), were used as received from the commercial package, and were placed directly on the contralateral eye of Dr. Becker. Thus, a side-by-side comparison of the ophthalmic compatibility of the Lai '461 lens versus the inventive lens could be investigated in the same individual, in a real-world ocular environment.[6]

28. After placing the lenses in the eyes as described above, video tape recordings were made using an S-VHS videocassette recorder to document the side-by-side comparison of the lenses. The performance of the lenses was documented using a diffuse and direct focal slit lamp illumination, listed and attached as Exhibit A, and a Tear Scope in the observational path of the recorder and the lenses, listed and attached as Exhibit B.

29. The video tapes were shown to the Examiner during an in-person interview conducted at the U.S. Patent & Trademark Office on June 1, 2000. At the request of the Examiner during the in-person interview, a separate test was further carried out where an inventive lens was placed on a HEMA lens which in turn was placed on the eye of Dr. Becker in the same piggyback manner as the Lai '461 lens was placed on a HEMA carrier lens. The piggyback experiment of the inventive lens showed that no adverse clinical observations were induced from the experimental protocol employed.

[6] The Lai '461 lens had a thickness of about 70 microns, the HEMA lens had a thickness of about 80 microns and the inventive Focus™ Night & Day® lens had a thickness of about 80 microns.

Attached and listed as Exhibit C is a VHS videocassette documenting the results of the inventive Focus™ Night & Day® on a HEMA lens.

30. Both Exhibits A and B, slit lamp and Tear Scope, of the side-by-side experiment demonstrated that lipid deposits formed on the Lai '461 lens in less than a minute. Exhibit B particularly illustrated that the Lai '461 lens was uniformly covered with lipid deposits within 2 1/2 minutes after placement of the lens in the eye of Dr. Becker.

31. In Exhibit A, under the slit lamp examination, the outer edge of the Lai '461 lens on the HEMA carrier was shown by an arrow. During filming, the VHS recorder was zoomed in on the Lai '461 lens to demonstrate that oil was blooming from the lens as Dr. Becker blinked indicating that the lipid source was the result of lipid deposition on the lens surface. As Dr. Becker continued to blink, the tear film on the Lai '461 lens would break off or shear away from the lens because the lens was not a wettable surface. The documented experiment demonstrated that the Lai '461 lens could not sustain a solid tear film in an ocular environment.

32. In Exhibit B, it can be seen that lipid deposits on the Lai '461 lens caused a marked haze to develop on the lens; it was no longer clear and crisp. The Tear Scope illumination of the lens showed an imperfect reflective surface off of the lens indicating light scatter which in turn results in poor vision from the lens. The reflective image of the light source should be a perfect image. However, the Lai '461 lens shows irregular, non-circular reflections from a perfect circular image source.

33. In stark contrast to the Lai '461, the inventive lens in the contralateral eye of Dr. Becker, during the same time period, showed no adverse clinical observations whatsoever. In fact, the inventive lens on the contralateral eye of Dr. Becker demonstrated perfect reflection of the light source, no lipid adsorption whatsoever, and furthermore, under the Tear Scope shown in Exhibit B, a perfectly round reflection of the light source was observed that was crisp and clear in a reflective mode. As further shown

in Exhibit B, the inventive lens demonstrated an unbroken, perfect tear film flowing over the entire inventive lens. The same advantageous results are seen in subsequent piggyback experiment of the inventive lens on a HEMA carrier, as documented in Exhibit C.

34. The side-by-side experimental results are statistically relevant and are unexpected and superior over Lai '461.

35. After removal of the Lai '461 lens from the eye of Dr. Becker, that eye remained irritated and "gritty" feeling for over eight hours (until sleep). In stark contrast, no adverse affect was observed in the eye containing the inventive lens. The irritation and gritty feeling was the result from the lipid adsorption and subsequent irritation from the Lai '461 lens. A unique, subsequent piggyback clinical evaluation of the inventive lens on top of a HEMA carrier did not result in any irritation or gritty sensation. Therefore, the gritty sensation and irritation is excluded from being an artifact of the clinical procedure.

36. The lenses were also evaluated In-Vitro whereby digital images of the lenses were taken under a darkfield microscope. Digital images were taken of the lenses before placement and after placement in the eyes of Dr. Becker to further document any protein or lipid deposits that occurred on either the inventive lens or the Lai '461 after being worn.

37. Attached and listed as Exhibit D is a digital image of an inventive lens before use and attached and listed as Exhibit E is a digital images of the Lai '461 taken before placement in the eyes of Dr. Becker.

38. Attached and listed as Exhibit F and Exhibit G are copies of the digital images of the inventive lens and the Lai '461 lens, respectively. The digital image of the lenses were taken after being in the eyes of Dr. Becker for five minutes, as received from the eyes, with no additional treatment or cleaning of the lens surface. Prior to taking the

images, the lenses were not conditioned in anyway. The lenses were kept hydrated in SoftWear™ saline.

39. The Lai '461 lens, after digital images were taken as shown in Exhibit G, was then treated with MiraFlow™ cleaner[7] and rinsed with SoftWear™ saline, in accordance with the manufacturer's instructions for those solutions. Attached and listed as Exhibit H is a copy of the digital image of the Lai '461 lens after being cleaned with MiraFlow™ and rinsed. The contralateral inventive lens worn by Dr. Becker, after digital images were taken as shown in Exhibit F, was then merely rubbed and rinsed with saline. For comparison, attached and listed as Exhibit I is a copy of the digital image of inventive lens worn by Dr. Becker after being rubbed and rinsed The saline rub and rinse was performed on the lens to demonstrate that there were optical artifacts present in the microscope apparatus, not on the lenses or caused from the experimental procedure.

40. Exhibits G and H were shown to the Examiner during the in-person interview where I hand wrote on the bottom of Exhibits G and H the expression "5 min" to indicate the time that the lens was in the eye of Dr. Becker.

41. The opacity of the lens surface, as seen by Exhibit G, demonstrates that significant amounts of lipids (and/or lipid with proteins) adhere to the Lai '461 lens. In fact even after the short five minutes of wear, significant lipid deposits is particularly evident when comparing Exhibits E and G, the digital images of the Lai '461 before and after five minutes of wear. Even after cleaning the Lai '461 lens with MiraFlow™ cleaner and rinsing with SoftWear™ saline, significant amounts of lipids (and/or lipid with proteins) tenaciously remain on the Lai '461 lens, as seen by Exhibit H. The high propensity for lipid deposits on the Lai '461 renders the lens unsuitable for use as an ophthalmic lens and unsuited for extended periods of wear.

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[7] MiraFlow™ is a contact lens cleaning solution containing detergents and isopropanol specifically formulated for removing lipid deposits. MiraFlow™ is a commercially available from CIBA Vision.

42. To further demonstrate the superiority of the inventive lenses over the Lai '461 lenses, I retrieved a set of inventive lenses used in clinical studies after over 40 days of continuous wear in the eyes of a subject. Attached and listed as Exhibits J and K are copies of the digital images of the clinically used lenses. The digital images of the lenses were taken after over 40 days of continuous wear, as received from the eyes, Exhibit J, and after a rub and rinse with SoftWear™ saline, Exhibit K. The saline rub and rinse was performed on the lens to demonstrate that there were optical artifacts present in the microscope apparatus, not on the lenses or caused from the experimental procedure.

43. Exhibits J and K were shown to the Examiner during the in-person interview where I hand wrote on the bottom of Exhibits E and F the expression "40 + day" or "40 + days" to indicate the time that the lenses were worn.

44. By comparing the inventive lens before placement, Exhibit D, to the inventive lens worn by Dr. Becker during the contralateral Lai '461 lens experiment, Exhibit F, and the worn inventive lens after a rub and rinse procedure, Exhibit I, as well as the clinically used lenses, Exhibits J and K, it is apparent that no significant lipid deposits form on the inventive lenses after their use in an ocular environment. In fact, no lipid deposits whatsoever were observed on any of the Focus™ Night & Day® lenses, including the Focus™ Night & Day® worn in excess of 40 days.

45. It is apparent from the above results that the lenses made according to the teaching of Lai '461 do not have ophthalmically compatible inner and outer surfaces.

46. It is further apparent from the above results that the lenses made according to the teaching of Lai '461 are not suited to extended periods of wear in continuous, intimate contact with ocular tissue and ocular fluids.

47. It is still further apparent from the above results that the lenses made according to the teaching of Lai '461 are not ophthalmically compatible.

48. It should be noted that the Heiler Declaration does not offer any data as to the ophthalmic compatibility or incompatibility of lenses made according to the materials of Lai '461.

49. Thus, it is factually apparent from the above results that the contact lenses made according to Lai '461 do not inherently possess the properties or structural features of the presently claimed ophthalmic lenses. The above results are statistically relevant and are unexpected and superior over Lai '461.

Surface Treatment

50. Based on the teachings of JP, the Examiner asserted that it is reasonable to expect that a plasma treated lens surface will acquire a relatively greater hydrophilicity as compared to the core portion of the lens. It was further asserted that a contact lens subjected to this treatment also acquires other advantageous properties such as stain resistance, wear comfort and biocompatibility.[8] It was then concluded that it would have been obvious to one of ordinary skill in the art to apply the plasma treatment process taught by JP alone or in combination with Hawley, to the surface of a contact lens formed from the polymeric materials disclosed by Lai.[9]

51. Initially, it should be understood that plasma processes are carried out at below ambient pressures to effect the plasma. As such, they are dry processes. Wet materials will not allow pressures low enough to "strike" a plasma due to the outgassing and evaporation of liquid from the material subject to the plasma treatment.

52. In such dry environments, the exposed surface polymer chains are not the steady-state equilibrium surface polymer chains that will be exposed to the tear film or any other aqueous environment. It is important to appreciate that surface modification of

[8] Office Action issued April 18, 2000.

[9] Office Action issued April 18, 2000.

a polymeric material is not necessarily fixed in that polymers have a propensity to reorient to accommodate different environments, particularly oxyperm polymerizable materials such as poly(dimethyl siloxanes) and poly(dimethyl siloxane) hydrogels.

53. To better understand polymeric materials useful in the ophthalmic arts, the following background discussion is provided.

54. Classical surface chemistry assumes that solid surfaces are rigid, immobile, and at equilibrium. These assumptions allow one to probe adsorption and wetting or contact angle processes purely from the point of view of the liquid phase, because it assumes that the solid phase does not in any way respond, reorient, or otherwise change in the different liquid environments. Although such assumptions may be partially correct for truly rigid solids, they are generally inappropriate for polymers (1).

55. However, In 1975 Holly and Refojo (2) set out the classical treatise on contact lens surface wetting behavior. Basically, they theorized polymer side chain reorientation influences the wetting properties of soft contact lenses. This theory has now become standard knowledge among surface scientists who engineer biocompatible materials.

56. Polymer structures and properties are, in general, time and temperature dependent. Because of the relatively large size and high molecular weights of synthetic polymer molecules, it is unlikely that most polymeric solids ever achieve a true equilibrium (3).

57. Solid polymers are, therefore, inherently non-equilibrium structures and as such exhibit a range of relaxation times and properties under normal conditions and in response to changing environments (4). As such, the ophthalmic community was aware, as early as 1975 that the surface of a polymer in an underwater environment may be, and

generally is, very different from the surface in air or other environments. This was the thrust of the Refojo and Holly surface-reorientation assertion in 1975.

58. Thus, the assumption that mere modification of a polymeric surface, by a plasma process, to produce a hydrophilic surface on a contact lens unrealistically disregards the teachings of polymer mobility and the natural tendency of a polymer to reorient its surface to accommodate a given environment to which it is exposed.

The Ocular Environment and Lipid Deposits

59. The Examiner is urged to appreciate that ocular fluids contained in the ocular environment are a dynamic, complex mixture comprising aqueous components as well as hydrophobic components, including lipids and lipoproteins. Ophthalmically compatible lenses suitable for this environment, in addition to being able to accommodate the aqueous environment, must not substantially accumulate lipid or protein deposits which deleteriously interferes with light transmissibility of the lens.

60. When a hydrophobic environment (or more accurately a hydrophobic microenvironment) is in close proximity to a mobile surface (such as the polymeric materials of the present invention), the surface will attempt to reorient so as to accommodate the hydrophobic phase, if possible.

61. It has been known that certain oxyperm materials, such as siloxane-containing polymers are highly lipophilic. The use of siloxane polymers as contact lenses results in the absorption of lipids and proteins on the lens from the ocular fluid deleteriously interfering with vision through the lens.[10]

62. Conventional plasma surface treatment processes do not overcome the known deficiencies of lipid and/or protein deposition in prior art contact lens materials.

[10] See, e.g. column 2, lines 11-22 of US 5,760,100; see also page 3, third paragraph of JP.

Conventional plasma process favor hydrophobic interactions. Therefore, the hydrophobic "core" of a polymer will be exposed to the plasma treatment. As the polymer is placed in an ocular environment, however, the plasma made hydrophilic surface will reorient "inside" the polymer matrix thereby exposing another hydrophobic surface due to interaction with the lipids present in tears of the ocular environment. This effect will result in a lens having a surface as though untreated by the plasma process or (worst case) totally hydrophobic.

63. The resultant non-treated areas (now exposed on the surface of the lens) will have undesirable surface properties and the material will end up unsuitable for a biomedical application or as a contact lens. Most specifically, the untreated areas will take up tear specific lipids.

Treatment of Silicone Containing Polymers

64. It was not obvious to one of skill in the art (such as Dr. Lai) to surface treat a silicone hydrogel material to achieve an ophthalmically compatible lens. This is borne out by the mere fact that Lai (in his 5,034,461 patent and several subsequent Lai patents on silicone hydrogels) make no mention of surface modification. The Lai polymers are described as "wettable", in that they absorb significant amounts of water into their bulk and therefore ophthalmic compatibility is assumed.

65. In fact, Dr. Lai acknowledged that plasma treatment was tried as early as 1989 at Bausch and Lomb on formulation 35:35:30 and that plasma treatment did not render the material suitable for use as a contact lens material.[11] Dr. Lai acknowledged that the issue with the plasma treated lenses was lipid deposit. Thus from Dr. Lai's testimony, it is apparent that Bausch & Lomb tried surface plasma treatment from 1989 to 1992 and were unable to achieve a lens that was devoid of lipid deposits[12].

[11] See page 254 of Dr. Lai's deposition testimony.

[12] See page 334 of Dr. Lai's deposition testimony.

66. Underscoring the non-obviousness of plasma treatment of silicon containing polymers, C. P. Ho and H. Yasuda published a research article typical of the knowledge at the time regarding methods of surface treating silicone elastomer, such as polydimethyl siloxane, in an attempt to produce contact lenses from those materials (5).

67. As a tear-lipid model, they utilized Sudan IV Red-dye to mimic lipid penetration onto and into the silicone elastomer surface and matrix, respectively. With oxygen plasma treatment of the silicone elastomer, Sudan IV red-dye staining of the core material was always evident. However, if they applied a methane plasma coating to the material no Sudan IV Red staining would occur once they achieved a specific coating thickness of the resultant polymerized methane-derived carbon.

68. In contrast to the inventive lenses, C. P. Ho and H. Yasuda teach that materials suitable for use as contact lenses should have a "closed network" coating that is highly crosslinked, thin (10nm), pin-hole free coating which "drastically reduces water permeability".

69. With silicone hydrogels, it was disclosed[13] that this lipid penetration phenomenon applies even more critically to silicone hydrogels; in that tear borne lipids can also adsorb onto the inner meshwork of a silicone hydrogel as well as onto the outer surfaces of the lens. With the present inventive ophthalmic lens surfaces, however, one can achieve successful wetting with no, or clinically insignificant, lipid adsorption. This is further illustrated in the previously described side-by-side performance study.

Failure of Conventional Plasma Surface Treatment

70. In an attempt to demonstrate the failure of conventional surface treatments, I replicated the surface plasma coatings of Ho and Yasuda (5) on the lens

[13] Column 2, lines 20-22 of US 5,760,100.

materials disclosed in an embodiment of US 5,760,100. I used the Alsacon material as disclosed in Example A-2 and the conventional plasma process of feeding methane gas in a Bransonic RF plasma reactor conditioned at 40 Watts of power and 50 mTorr of pressure. The methane was fed to the reactor at two standard cubic centimeters per minute (sccm). Every plasma processed lens was wettable, in that it held a uniform water film on the eye.

71. However, the lenses coated from the conventional methane plasma according to Ho and Yasuda resulted in a hardened polymerized-carbon surface that crazed (i.e. fractured) upon hydration. This fractured coated surface adversely scattered light rendering the optics of the coated lens unsuitable for use as an ophthalmic lens.

72. A further illustration of the deficiencies of conventional plasma processes in rendering ophthalmic compatible lenses is demonstrated by the following experiment.

73. Lenses prepared according to Examples B-5 and E-12 of the 5,760,100 patent (CIBA Vision's Focus® Night & Day™ lenses), for example, were treated with a trimethyl or tetramethylsilane (TMS)[14] plasma process. For reference, the uncoated material has a contact angle of from 110 to 120 degrees. Using trimethyl or tetramethylsilane (TMS) plasma to coat the lens material provides the following results:

74. Table-I. Wettability test with water contact angle meter (0.5 μl)

		4-min	7-min	10-min	14-min
water contact angle	deg.	105	110	109	101
sessile drop height	mm	0.613	0.624	0.687	0.536
sessile drop area	mm^2	0.756	0.688	0.766	0.587

75. It is apparent from Table I that the contact angles do not drop significantly upon conventional plasma treatment of the surface of the materials. The results are

[14] The biomedical literature often uses the control surface coating of trimethylsilane or tetramethylsilane as a hemocompatible surface for biomaterials.

indicative of surfaces that will not exhibit better wetting character after plasma treatment. This further illustrates the deficiencies in conventional plasma surface processes to treat contact lenses to obtain ophthalmically compatible surfaces.

Compatible Ophthalmic Lenses

76. In contradistinction to the conventional teachings at the time of Lai's disclosure (5), it was discovered and disclosed by the inventive entity of the present reexamination patent that any coating made on contact lens materials needs to allow Ion/water permeation, rather than drastically reduce it, as previously taught.

77. As illustrated in embodiments Examples B-12 and E-1 of US 5,760,100, the invention teaches how to modify lens materials to successfully achieve ophthalmically compatible inner and outer surfaces. The ophthalmic surfaces achieved in practicing the present invention yield a structural surface suitable for extended periods of wear in continuous, intimate contact with ocular tissue and ocular fluid. As ophthalmically compatible surfaces, the inventive lenses are free of adverse lipid adsorption.

Testing of Ophthalmic Lenses

78. It was noted by the inventors of present reexamination patent that different test protocols resulted in different values when determining oxygen permeability.[15] The subject reexamination patent disclosed that the oxygen permeability of a material was determined by the coulometric method.[16] The coulometric method was chosen because unlike other methods, such as a polarographic method, the coulometric method can accurately measure permeabilities above 70 barrers (Dk units). In fact, it has been

[15] It was noted that wet and dry measurements of oxygen permeability differ greatly (See, for example, column 51, beginning on line 19 of US 5,760,100).

[16] See, column 51, lines 28-40 of US 5,760,100.

published (7) that the polarographic method cannot measure accurately above 70 barrers (Dk units).

79. Underscoring the consistency of the coulometric method, the ISO/CD 9913-2 *draft*, DIN 53380, ASTM 3986-81, ASTM 1434-75 and JIS K 7126 (1987) have all certified this technique as a primary standard. Intra-lab variances of 1-3 percent and inter-lab differences of from 3-5 percent are expected and validated.

80. Using a Dk1000 instrument (available from Applied Design and Development Co., Norcross, Ga.),[17] oxygen permeability was determined in accordance with the following testing procedures.[18]

81. Oxygen fluxes (J) are measured at 34 C in a wet cell (i.e., gas streams are maintained at about 100% relative humidity) using a Dk1000 instrument (available from Applied Design and Development Co., Norcross, Ga.), or similar analytical instrument. An air stream, having a known percentage of oxygen (e.g., 21%), is passed across one side of the lens at a rate of about 10 to 20 cm^3 /min., while a nitrogen stream is passed on the opposite side of the lens at a rate of about 10 to 20 cm^3 /min. The barometric pressure surrounding the system, $P_{measured}$, is measured. The thickness (t) of the lens in the area being exposed for testing is determined by measuring about 10 locations with a Mitotoya micrometer VL-50, or similar instrument, and averaging the measurements. The oxygen concentration in the nitrogen stream (i.e., oxygen which diffuses through the lens) is measured using the DK1000 instrument. The oxygen permeability of the lens material, D_k, is determined from the following formula:

$$D_k = Jt/(P_{oxygen})$$

where J = oxygen flux [microliters O_2 /cm^2 -minute]

$$P_{oxygen} = (P_{measured} - P_{water\ vapor}) = (\%O_2 \text{ in air stream}) \text{ [mm Hg]}$$

= partial pressure of oxygen in the air stream

[17] A DK1000 instrument was used for coulometric measurements, see, generally column 15 under section G and Example A-1 of US 5,760,100.

[18] See, for example, column 15 under G of US 5,760,100.

$P_{measured}$ = barometric pressure [mm Hg]

$P_{water\ vapor}$ = 0 mm Hg at 34 C (in a dry cell) [mm Hg]

$P_{water\ vapor}$ = 40 mm Hg at 34 C (in a wet cell) [mm Hg]

t = average thickness of the lens over the exposed test area [mm]

where D_k is expressed in units of barrers, i.e., [(cc oxygen)(mm)/cm^2)] x [sec/mm Hg] x 10^{-10}.

82. It should be noted that the Heiler Declaration employed the polarographic method in determining oxygen transmittability of the Lai '461 materials.[19] According to Dr. Heiler, when oxygen transmissibility is expertly measured using the polarographic technique, its precision is no better than about ±15%; and when the degree of expertise applied to measure an oxygen transmissibility number is unknown, its precision is generally considered to be no better than about ±20%.[20] This declaration, in conjunction with the previously published findings (7), illustrate why the coulometric method was chosen as the only appropriate measurement tool that could be accurately employed for silicone hydrogels whose Dk exceeds 70 barrers.

83. It was discovered that the ophthalmically compatible lens of the present invention requires ion permeability for extended wear. However, ion permeability was not considered a matter of routine testing in the industry at the time of filing the patent.[21] Thus, methods were developed and disclosed for testing ion permeability. In describing the Ionoflux measuring technique,[22] the expression "Ionoflux Ion Permeability Coefficient" and "Ionoflux Diffusion Coefficient" were used interchangeably (emphasis added). Each expression is a "Coefficient" defined by the units of mm^2/min and is used

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[19] See Heiler Declaration page 3, paragraph 7.

[20] See Heiler Declaration page 4, paragraph 8.

[21] See for example the disclosure of US 5,760,100, column 10, lines 25-30.

[22] See, for example, column 10, beginning at line 56 of US 5,760,100.

to identify the rate of "ion permeability" through a lens.[23] This interchange of coefficient terms is appropriate, as both describe the inherent property of the entire lens construct.

84. Ionoflux diffusion coefficients were determined in accordance with the testing procedures described in the subject patent.[24]

85. The "Ionoflux Technique" involves the use of a conductometer (LF 2000/C, catalog no. 300105, Wissenschaftlich-Technische Werkstatten GmbH (WTW), Germany), an electrode equipped with a temperature sensor (LR 01/T, catalog no. 302 520, WTW), a donor chamber containing a salt solution, a receiving chamber containing about 60 ml of deionized water, a stir bar and a thermostat.

The donor chamber is specially designed for sealing a contact lens thereto, so that the donor solution does not pass around the lens (i.e., ions may only pass through the lens). The donor chamber is composed of a glass tube which is threaded at the end which is immersed in the receiving solution. The glass tube includes a centrally located hole of about 9 mm in diameter. A lid, which is threaded to mate with the glass tube, holds a lens-retaining member which includes a centrally located hole of about 8 mm in diameter. The lens-retaining member includes a male portion adapted to mate with and seal the edges of the inner (concave) surface of a lens and a female portion adapted to mate with and seal the edges of the outer (convex) surface of a lens.

The lens to be measured is placed in the lens-retaining member, between the male and female portions. The male and female portions include flexible sealing rings which are positioned between the lens and the respective male or female portion. After positioning the lens in the lens-retaining member, the lens-retaining member is placed in the threaded lid. The lid is screwed onto the glass tube to define the donor chamber. The donor chamber is filled with 16 ml of 0.1 molar NaCl solution. The receiving chamber is filled with 60 ml of deionized water. The leads of the conductivity meter are immersed in the deionized water of the receiving chamber and a stir bar is added to the receiving chamber. The receiving chamber is placed in a thermostat and the temperature is held at about 35 °C. Finally, the donor chamber is immersed in the receiving chamber.

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[23] See, for example, Examples F1-F12; column 67, lines 42-58 of US 5,760,100.

[24] See, for example, column 10 beginning on line 56 of US 5,760,100.

Measurements of conductivity are taken every 20 minutes for about three hours, starting 10 minutes after immersion of the donor chamber into the receiving chamber. The Ionoflux Diffusion Coefficient, D, is determined by applying Fick's law as follows:

$$D = -n'/(A \times dc/dx)$$

where n' = rate of ion transport (mol/min)

A = area of lens exposed (mm^2)

D = Ionoflux Diffusion Coefficient(mm^2 /min)

dc = concentration difference (mol/L)

dx = thickness of lens (mm)

86. Ionoton ion permeability coefficients were determined in accordance with the testing procedures described in the subject patent.[25]

87. The "Ionoton Technique" involves the use of a pH meter (Beckman, VWR catalog no. BK123142), a VSC-1 Diffusion Cell Drive Console (Crown-Bio, Somerville, N.J.), a DCB-100B Diffusion Cell (Crown-Bio), and a 6 cm sodium ion-specific electrode (Microelectronics, Londonderry, N.H., catalog no. MI-414P). The technique is not limited to the aforementioned instruments or materials; equivalent instruments or materials may be used.

First, a contact lens is mounted onto an orifice of the DCB-100B cell chamber, the donor chamber. Next, the connecting cell chamber (receptor chamber) is placed against the cell chamber containing the contact lens and tightly clamped on the clamp holder supplied with the VSC-1 Drive Console. Then, a phosphate-buffered saline (PBS, Mediatech catalog no. 21-031-LV) is placed into the receptor side of the cell chamber. Stir bars are added to each cell chamber. The 6 cm electrode is placed into the PBS saline receptor side. After the electrode has equilibrated in the PBS saline, the pH meter is placed in the mV function to establish the 0 mV point. PBS which has been saturated with sodium chloride is added to the donor chamber.

The millivolt signal is recorded at 5, 10, 15, 30, 60, 120, and 180 minute intervals. The millivolt signal is converted to a sodium ion concentration

[25] See, for example, column 11 beginning on line 51 of US 5,760,100.

by a standard curve of sodium ion concentration vs. millivolt signal. The Ionoton Ion Permeability Coefficient, P, is then determined in accordance with the following equation:

$$\ln(1-2C(t)/C(0)) = -2APt/Vd$$

where: C(t)=concentration of sodium ions at time t in the receiving cell

C(O)=initial concentration of sodium ions in donor cell

A = membrane area, i.e., lens area exposed to cells

V = volume of cell compartment (3.0 ml)

d = average lens thickness in the area exposed

P = permeability coefficient

The average thickness of the lens in the exposed test area may be determined by averaging a number of readings, e. g., 10 readings, with a low-pressure thickness-measuring instrument, such as a Mitotoya micrometer VL-50, or equivalents thereof. The Ionoton Ion Permeability Coefficient, P, having units of cm^2 /second, may be determined from the slope of a plot of time (t) v. $\ln(1-2C(t)/C(0)) \times (-2At/Vd)$.

Rejection Based on the JP 6-122779

88. Turning now to the rejection predicated on the English language translation of JP 6-122779 (hereinafter JP) cited by the examiner, my understanding of this reference is as follows.

89. On page three of JP, the reference discloses a surface-improved contact lens, particularly a contact lens whose surface has excellent hydrophilicity, stain resistance, and biocompatibility. On the bottom of the next page, JP discusses deficiencies of a hydrophilic surface in that such surfaces adhere proteins (see bottom of page 4 and the top of page 5 of JP).

90. The "stain" that JP refers to, in actuality, is denatured protein, lipid, or protein/lipid deposits that can buildup on a contact lens surface. On page 5, JP discusses

published unexamined patent applications that disclose methods for improving wettability by plasma treatment. JP then summarily dismisses the prior art processes as not making true improvements (first sentence of the first full paragraph on page 5 of JP).

91. The JP references teaches the deficiencies of the prior art in that "[a]s for the method disclosed in Published Unexamined Application No. 63-40293 the contact lens surface is simply plasma-treated to make it hydrophilic; therefore, hydrophilic groups are quickly hidden in the resin and lose the effect of making the surface hydrophilic. In addition, even though this method improves hydrophilicity, it does not improve wear comfort and stain resistance." This assertion is consistent with the discussion I have provided above.

92. The JP reference is thus consistent with the arguments and data present in the present Declaration. I understand JP to disclose that mere plasma process to improve wettability is not sufficient to overcome lipid adsorption, i.e. "staining", and that although wettability is necessary for an ophthalmically compatible lens it is an utterly insufficient criterion in the determination of ophthalmic compatibility.

93. What JP teaches can be summarized on page 6, line 9: "More specifically, the present invention graft-polymerizes a hydrophilic monomer that is a component resembling an in vivo substance on the contact lens surface, thus providing a contact lens that exhibits excellent hydrophilicity and stain resistance as well as dramatically improved wear comfort and that also has excellent biocompatibility."

94. According to JP, "[t]o attain the objective of the present invention, a specific hydrophilic monomer must be graft-polymerized on the surface of a contact lens." (page 7 of JP). In practicing the JP methods, the JP reference cites that corona discharge in air is enough to "activate" radicals or groups on the surface of the lens for grafting hydrophilic monomers.

95. Further on page 9, JP discloses that "[t]he contact lens of the present invention is obtained by graft-polymerizing the aforesaid hydrophilic monomers on the contact lens surface by a conventional method. Namely, the contact lens is subjected to a plasma treatment or corona-discharge treatment in air or in an oxygen ambience so as to generate active species, and the treated contact lens is immersed in a hydrophilic monomer solution to implement a graft polymerization."

96. The Examiner asserts that from this reference, "[s]ince the plasma treatment is applied to the lens, it is reasonable to expect that the surface acquires a relatively greater hydrophilicity as compared to the core portion of the lens". It was further asserted, based on the teaching of JP, that "[o]f significance is the recognition in the art that the plasma treatment process, in and of itself, renders a contact lens surface hydrophilic".[26]

97. These assertions and assumptions are contrary to the teaching of JP and manifestly inaccurate. As discussed above, JP discloses that simply plasma-treating the surface of a lens with the intent of making the lens hydrophilic will lose the effect of making the surface hydrophilic because the hydrophilic groups are quickly hidden in the resin.

Failure of Combining Lai with JP

98. It is not reasonable to expect that immersing the hygroscopic polymer materials (as taught by Lai '461) in a hydrophilic monomer solution (as taught by JP) would successfully produce an ophthalmically compatible lens, even if there were some suggestion in the art to do so.

99. To demonstrate that combined teaching of Lai with the teaching of JP fails to provide an ophthalmically compatible lens, the following experiment was carried out

[26] See, the Office Action issued April 18, 2000.

by me or under my direct supervision. Two of the Lai '461 40:30:30 lenses prepared by Drs. Hung and Wang (noted above) were first completely dried in vacuum (<0.1inch mmHg) at room temperature for two hours.[27] The lenses were then introduced into a plasma chamber (a PLASMOD radio frequency plasma unit, made by MARCH Instruments, California) A vacuum was introduced to the system for approximately 1 minute at 0.1mmHg. Oxygen gas was then allowed to enter the chamber for two minutes at a constant flow rate; which increased the vacuum to 1.1 Torr. A plasma was then struck using 25 watts reflective power for two minutes time. The power was then turned off and the chamber brought to ambient pressure with room air. Each lens was then removed from the plasma chamber and placed in a 20 ml glass vial filled with approximately 15 ml of a 20% acrylamide monomer/UV initiator solution immersing the lenses in the solution.[28] The two solutions, containing the lenses, were then degassed by bubbling nitrogen gas into the solution for 3 minutes and then polymerized under UV light for 1.5 minutes. The lenses were then removed from the vials and rinsed with water. Both lenses were fragile and exceptionally large, about 100% larger, after polymerization even after equilibrating in water. Thus, it is apparent that acrylamide monomer did graft onto the lens surface as well as to the *inside* meshwork of the lens. This grafting inside the lens matrix resulted in the lens swelling up to twice its normal size rendering the graft-polymerized lens unusable as a contact lens. This experiment illustrates that grafting monomer to a lens-shaped article cannot convert a hydrophobic lens to an ophthalmically compatible contact lens.

JP 6-122779 in Combination with Hawley

100. It was asserted that JP discloses subjecting a contact lens surface to a plasma treatment in air or oxygen ambience. Hawley's Condensed Chemical is then cited

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[27] It was necessary to dry the lens before plasma treatment because a plasma could not be generated with wet lenses.

[28] The acrylamide solution contained 20% (w/v) acrylamide in ethanol together with 0.2% of the free radical initiator Darocur 1173. The 0.2% of Darocur was based on the weight of acrylamide.

to establish that air is but a mixture of such gases as nitrogen, oxygen, argon and methane, among others.[29]

101. Repeatedly, it is stressed that JP does not teach mere surface plasma treatment. Rather JP teaches the use of a plasma to activate the surface of a contact lens so that grafting hydrophilic monomers to the activated surface can be accomplished.

102. It should further be noted that Hawley's definition states that air is "[a] mixture (or solution) of gases, the composition of which varies with altitude and other conditions at the collection point." No commercial process would rely on a composition that can vary with the most important species necessary for the plasma process.

103. Partly because of the variations in air, we have defined air to denote 79% nitrogen and 21% oxygen in practicing the plasma process.[30]

104. Further, Hawley defines air as containing methane in 2 parts per million[31] *by volume* (exclusive of water vapor). This modicum of methane is equivalent to 2 cc of methane in 10,000 liters of air. For a methane plasma process that requires 2 cc per minute of methane, the process would require 10,000 liters per minute of air to enter the vacuum plasma chamber and yet still maintain a vacuum.[32] Virtually impossible for any plasma system. Furthermore, even were this achievable, one would still have to separate the two cubic centimeters of methane species from the 10000 liters of other gasses to prevent total etching of the lens surface and obtain the desired polymerization of methane on the lens surface. This is another unattainable task in a manufacturing environment.

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[29] See, the Office Action issued April 18, 2000.

[30] See, for example, US 5,760,100 column 53, Example B-12; column 58, and Example C-21.

[31] Hawley defines dry air as a composition containing methane at 0.0002 % by volume.

[32] CIBA Vision's typical plasma processes use about one to about three total standard cubic centimeters per minute (sccm) of a given gas.

The methane concentration (as disclosed in Hawley) is utterly insufficient for any coating to occur in any environment.

References

1) J. D. Andrade, L.M. Smith and D. E. Gregonis "The Contact Angle and Interface Energetics" in Surface and Interfacial Aspects of Biomedical Polymers, Volume One, Surface Chemistry and Physics, Plenum Press 1985
2) F.J. Holly and M.F. Refojo Wettability of hydrogels, JBMR 9, pp315-326, 1975
3) J. D. Andrade, D. E. Gregonis and L.M. Smith "Polymer Surface Dynamics" in Surface and Interfacial Aspects of Biomedical Polymers, Volume One, Surface Chemistry and Physics, Plenum Press 1985
4) P. Hedvig, Dielectric Spectroscopy of Polymers, Wiley, New York, 1977
5) Chung-Peng Ho and H. Yasuda, "Ultrathin coating of plasma polymer of methane applied on the surface of silicone contact lenses." JBMR, 22, pp. 919-937 1988.
6) V. Franklin and B. Tighe "A study of the Spoliation Profiles of High Dk Fluorosiloxane Hydrogel Lenses" BCLA, May 2000
7) B.A. Holden, J. Newton-Howes, L. Winterton, I. Fatt, H. Hamano, D. La Hood, N. Brennan, and N. Efron "The Dk Project: An Interlaboratory Comparison of Dk/L Measurements" Optometry and Vision Science 67(6), 1990 pp. 476-481

105. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11 July 2000
Date

Lynn C. Winterton

LIST OF EXHIBITS

A. S-VHS Videocassette record documenting the slit lamp illumination data of the ophthalmic compatibility results of the Lai '461 lens.

B. S-VHS Videocassette record documenting the Tear Scope data of the side-by-side comparison of the ophthalmic compatibility results of the Lai '461 lens versus the inventive lens in the same individual in a real-world ocular environment.

C. S-VHS videocassette documenting the results of the inventive Focus™ Night & Day® on a HEMA carrier lens.

D. Copy of a digital image produced under a darkfield microscope of the inventive lens taken before use.

E. Copy of a digital image produced under a darkfield microscope of the Lai '461 lens taken before placement in the eye of Dr. Becker.

F. Copy of a digital image produced under a darkfield microscope of the inventive lens taken after being in the contralateral eye of Dr. Becker for five minutes.

G. Copy of a digital image produced under a darkfield microscope of the Lai '461 lens taken after being in the eye of Dr. Becker for five minutes.

H. Copy of a digital image produced under a darkfield microscope of the Lai '461 lens of Exhibit G taken after washing with MiraFlow™ cleaner and rinsing with SoftWear™ saline.

I. Copy of a digital image produced under a darkfield microscope of the inventive lens of Exhibit G taken after a rub and rinse with saline.

J. Copy of a digital image produced under a darkfield microscope of the inventive lens taken after over 40 days of continuous wear, as received from the eye.

K. Copy of a digital image produced under a darkfield microscope of the inventive lens of Exhibit I taken after a rub and rinse with SoftWear™ saline.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of DECLARATION OF LYNN WINTERTON UNDER 37 C.F.R. § 1.132 w the Requester:

George Wheeler
McAndrews, Held & Malloy, Ltd.
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Suite 3400
Chicago, Illinois 60661
(312) 707-8889

by U.S. First Class mail on this 11th day of July, 2000.

Kenneth L. Cage